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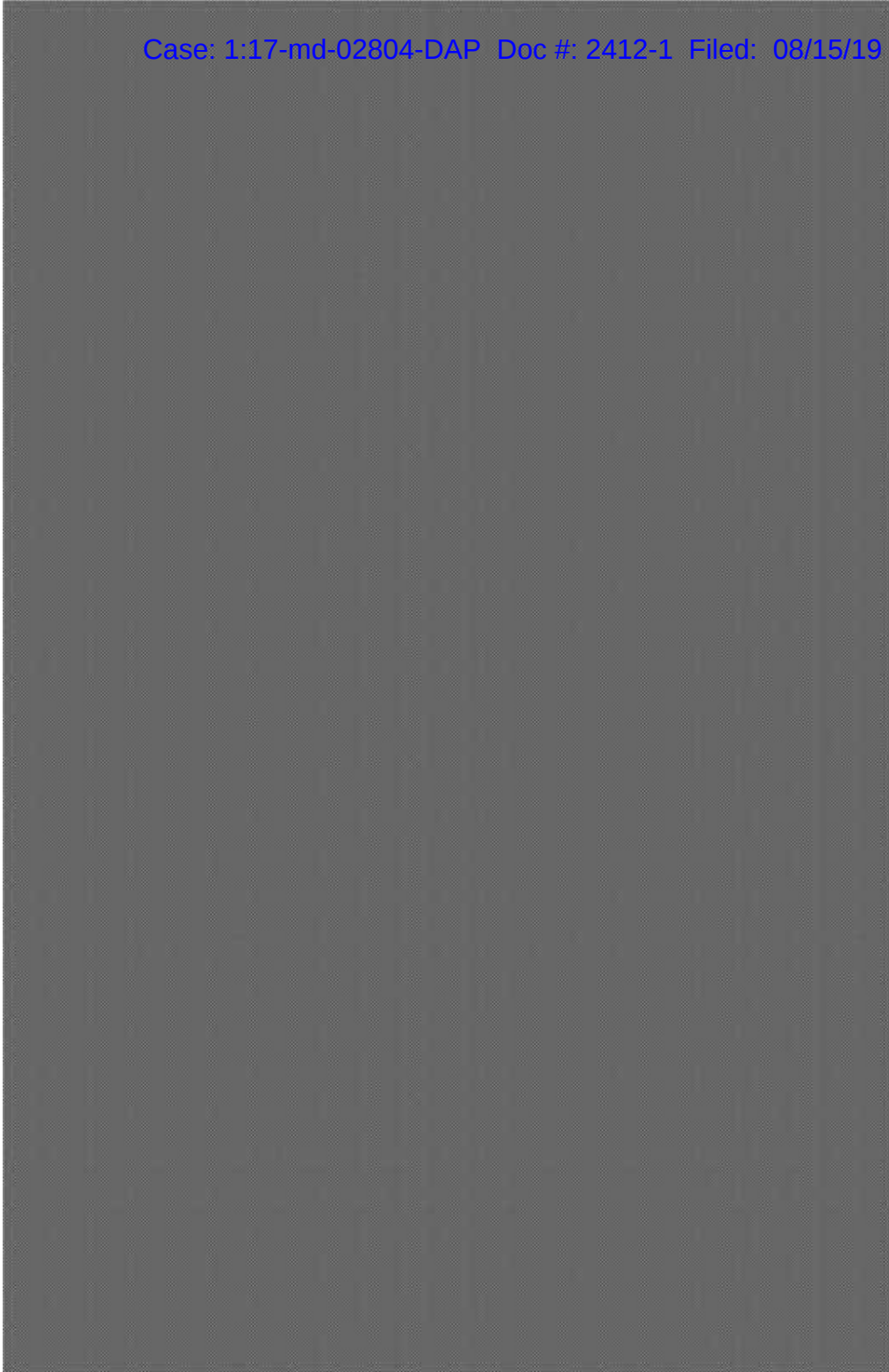
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CLINICAL ISSUES IN OPIOID PRESCRIBING

Considerations for the practitioner in the use of opioids in
managing moderate to severe pain



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CLINICAL ISSUES IN OPIOID PRESCRIBING

Opioids are an effective and established treatment for moderate to severe pain. Yet they are frequently underdosed — or even withheld due to a widespread lack of information and appropriate education about their use among healthcare professionals. Underuse of opioid analgesics and other treatments for pain has prompted pain expert C. Stratton Hill, MD, to declare: "All types of pain in all parts of the world are inadequately treated."*

"Clinical Issues in Opioid Prescribing" offers information on many of the most important issues related to appropriate prescribing and dosing of opioids for moderate to severe pain. Clear understanding and discussion of the concepts highlighted in this booklet can help pave the way for more effective opioid therapy in appropriate patients.

* Hill CS Jr. [editorial.] *JAMA*. 1995;274:1881-1882.

KEY TERMS IN PAIN MANAGEMENT**Addiction**

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.¹

Physical Dependence

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist.¹

Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.¹

Pseudoaddiction

Pseudoaddiction is a term which has been used to describe patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when the pain is effectively treated.¹

Misunderstanding of this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label 'addict.' ... In the setting of unrelieved pain, the request for increases in drug dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels.²

Key Terms References: 1. *Definitions Related to the Use of Opioids for the Treatment of Pain.* A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine, February, 2001. 2. Cherny NI. Opioid analgesics: Comparative features and prescribing guidelines. *Drugs*. 1996;51:713-737.

- 1 Respiratory Depression** *Does the risk of respiratory depression make opioids too dangerous?*
- 2 Addiction** *What is the risk of addiction associated with opioids used to treat patients with moderate to severe pain?*
- 3 Tolerance** *Does development of tolerance to opioids necessitate increasingly higher doses?*
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Does the risk of respiratory depression make opioids too dangerous?



While respiratory depression is the most serious risk with all opioid agonist preparations, clinically significant respiratory depression rarely occurs in patients treated for pain, when opioid doses are appropriately prescribed, administered, and titrated to effect.¹

The federal Agency for Healthcare Research and Quality (AHRQ), in its Clinical Practice Guideline for the management of cancer pain, states that “patients receiving long-term opioid therapy usually develop tolerance to the respiratory depressant effects of these agents.”²

If opioid doses are gradually increased, high dosages are generally well tolerated and not associated with respiratory depression.³ Studies in cancer patients have shown that when morphine is properly titrated against pain, respiratory failure is “neither common nor severe.”⁴

Respiratory depression is rare in patients who have been receiving chronic opioid treatment. It can occur, however, in opioid-naïve patients with severe pain who require high opioid doses.^{5,6}

In the absence of underlying pulmonary dysfunction, clinically significant respiratory depression is rarely seen when morphine doses are properly titrated.⁷ However, morphine and related opioids must be used cautiously in patients with compromised respiratory function including emphysema or cor pulmonale.⁷ In patients with chronic cor pulmonale, therapeutic doses of morphine have even caused death.⁷

**What is the risk of addiction associated
with opioids used to treat patients with
moderate to severe pain?**



In a 2001 consensus document, the American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine provide the most current thinking on often-confused terminology in pain medicine. The following is an excerpt:⁶

“Most specialists in pain medicine and addiction medicine agree that patients treated with prolonged opioid therapy usually do develop physical dependence and sometimes develop tolerance, but do not usually develop addictive disorders. However, the actual risk is not known and probably varies with genetic predisposition, among other factors. Addiction, unlike tolerance and physical dependence, is not a predictable drug effect, but represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals. ... Addiction is a primary chronic disease and exposure to drugs is only one of the etiologic factors in its development.

“Addiction in the course of opioid therapy of pain can best be assessed after the pain has been brought under adequate control, though this is not always possible. Addiction is recognized by the observation of one or more of its characteristic features: impaired control, craving and compulsive use, and continued use despite negative physical, mental, and/or social consequences.”

The consensus statement also stresses that behavior that may suggest addiction is sometimes in reality a reaction to unrelieved pain or is an indication of problems unrelated to addiction.⁸ Good clinical judgment

is required to assess whether or not a certain behavior set indicates true addiction or reflects other issues.⁸ (For *Definitions of Key Terms*, see page 2).

Pain expert C. Stratton Hill, Jr, MD, has noted that “scientific data show that almost all patients with painful medical conditions requiring opioids for treatment discontinue their use after the medical condition for which opioids were needed no longer exists.”⁹

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy,^{6,10} and proper dispensing and storage are appropriate measures that can help limit abuse of opioid drugs.¹⁰

It should be noted that, among terminally ill patients with pain, concern about addiction is largely irrelevant and may interfere with proper palliative care.^{11,12}

While preventing drug abuse is an important societal goal, there is consensus, by law enforcement agencies, healthcare practitioners, and patient advocates alike that it should not hinder patients’ ability to receive the care they need and deserve.¹³

Does development of tolerance to opioids necessitate increasingly higher doses?



When discussing tolerance in the context of opioid therapy, it is important to differentiate between analgesic tolerance and tolerance to non-therapeutic adverse effects.

Analgesic Tolerance

“Clinical experience indicates that tolerance to opioid therapy (i.e., the continued need for dose escalation to maintain the same level of pain relief in the absence of disease progression or other external factors) does not represent a common or major impasse in pain medicine.”¹⁴

Analgesic tolerance is an important element in the concept of opioid responsiveness.³ If a patient complains of increasing pain which is traced to disease progression or other sources, opioid analgesic tolerance cannot be inferred.³ Conversely, if dose escalation is required “in the absence of other obvious causes, tolerance may be the explanation.”³ Thus, while increasing dose requirements are most consistently correlated with progressive disease, stable disease does not usually require increasing doses.²

With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the most serious of which is respiratory depression.²

Tolerance to Opioid Adverse Effects

Even if opioid doses need to be gradually increased in a patient, common adverse effects may often decrease.¹ Sedation is a frequent side effect of initial opioid administration, but tolerance to this effect usually develops rapidly. Sedation may also be a transitory side effect when opioid doses are increased substantially, but tolerance to sedation usually develops quickly in these instances as well.² Tolerance also may develop quickly to the nausea and vomiting that can be common side effects of initial opioid therapy or when opioid doses are increased.¹

Most patients, however, do not develop tolerance to constipation, which is a universal side effect of treatment with opioids.² (See the following page for a detailed discussion of opioid-induced constipation.)

**When opioids are dosed adequately
to control pain, does constipation become unmanageable?**



While constipation is a nearly universal side effect of opioid treatment—oral, transdermal or parenteral—it can be effectively managed. Constipation is not a reason to withhold opioid pain control from patients who need it.^{1,2}

The AHRQ recommends a bowel protocol for patients who may experience marked constipation when taking opioids, which includes administering a stimulant laxative agent.²

Oral laxatives can be taken at bedtime, and rectal suppositories used in the morning if needed.² Stool softeners, while not useful alone, are effective in combination with stimulant laxatives, to allow water to enter hard, dry stools. Laxatives should be taken under a physician's direction.

Is routine prophylactic antiemesis required for the majority of patients taking opioids?



While nausea can be a common side effect of opioid treatment for pain, it is usually transient and typically diminishes over the first few days of therapy.¹

In patients taking opioids, it is important to determine the cause of nausea and vomiting.^{1,2} Sometimes, and particularly in cancer patients, nausea and vomiting can result from chemotherapy or disease progression, not just from opioid therapy.^{1,2}

Nausea and vomiting should be managed according to the underlying cause. As the AHRQ notes, antiemetics can be used “when patients complain of nausea after opioid administration has begun.”²

To manage nausea and vomiting, antiemetic therapy can be administered on a fixed schedule for several days.² After that, the dose of antiemetic can usually be provided on an as-needed basis.² Ultimately, antiemetic therapy may be discontinued as nausea and vomiting is alleviated.^{1,2} Relief of constipation can also help mitigate nausea.^{1,2}

Prophylactic antiemetic therapy is discouraged due to associated sedation and other potential side effects.¹

Is sedation a common and/or unmanageable side effect associated with opioid therapy?



Although sedation or somnolence is a frequently reported side effect of opioid therapy, it is usually self-limited and does not persist beyond the first few days of treatment.^{1,2}

Typically, sedation occurs after initiation of opioid therapy or after upward titration to a new dose, after which tolerance usually develops.^{1,6} If sedation persists, patients and prescriber can work together to titrate a dosage that balances pain relief and side effects.⁶

Sedation is a common effect when patients initially receive opioid analgesics or after a significant increase in dose. This usually improves over the first few days. In cancer patients who are taking opioid medication, there are often other possible causes or contributors to sedation such as infection, metabolic disturbance, renal impairment, dehydration, CNS involvement, or concomitant use of other sedative drugs. Underlying contributing factors should be addressed.⁶

Patients should be advised that opioids may impair mental and/or physical ability required for the performance of potentially arduous tasks (e.g., driving operating heavy machinery), and these activities should not be attempted until a patient knows how a given opioid affects alertness.

What is the most appropriate opioid dosing schedule for controlling moderate to severe pain?



In choosing an appropriate analgesic dosing schedule to treat pain, it is important to assess both intensity and duration. Duration may be reasonably predicted, as with postsurgical or postinjury pain, or may become relatively unpredictable. When choosing an effective dosing schedule, one must also consider pain intensity, often characterized as mild, mild to moderate, moderately severe, or severe.^{2,6,15-17}

Any proposed systemic regimen must be individualized for the patient, and inflexible reliance should not be placed on any “standard” mixture of medications and/or dosing regimens. For patients with moderate or severe pain, opioid therapy is recommended. Once an opioid and a route of administration are chosen, the dose should be increased until a favorable response occurs or when unmanageable or intolerable adverse effects ensue.¹⁵

Please note that while precise definitions of many terms commonly used to characterize pain remain a topic of international discussion, those used here are taken from sources relevant to the topic of opioid dosing schedules.

Acute pain is most often associated with injury to the body (e.g., surgery, trauma, etc.); it decreases over time and resolves with healing.¹⁶

There is no universal agreement on when an acute pain state ends and the pain becomes **chronic**. However, the two chronologic markers most commonly used to identify pain as chronic are 3 months and 6 months since the onset of pain,¹⁶ although these distinctions are described as arbitrary.¹⁶ Often the cause of chronic pain cannot be removed or otherwise treated and it may be associated with a long-

term, incurable condition.¹⁶

In temporal terms pain can also be described as **persistent**—existing continuously [throughout the day] or as **intermittent**, also referred to as recurrent pain.¹⁶ Intermittent or recurrent pain is episodic, with each episode lasting a relatively short period of time but recurring over an extended period of time (e.g., sickle cell crisis).¹⁶ In some cases, recurrences may be separated by completely pain free periods (e.g., migraine).¹⁶

Opioid medications are the major class of analgesics used to treat **moderate to severe pain**, whether acute, intermittent, persistent, or chronic.^{2,5}

When treating **persistent** pain that is either acute or chronic, the ideal opioid dosing schedule is one that not only relieves pain, but that also prevents it from returning.² The AHRQ recommends that persistent or daily pain that is moderate to severe be treated with opioids “on a regular schedule rather than only ‘as needed.’” An “around-the-clock” (ATC) fixed-dosing schedule is preferred to PRN dosing because it helps maintain a constant blood level of medication, which helps prevent the recurrence of pain.^{2,5} ATC “administration of analgesics allows each dose to become effective before the previous dose has lost its effectiveness.”²

Acute persistent pain that is moderate to severe, such as initial post-surgical pain, is also best initially treated on a regular, around-the-clock schedule.¹⁷

For patients taking controlled-release opioids on a fixed dose, around-the-clock schedule, it is recommended that a supplementary immediate-release medication be provided to treat exacerbations of pain that may occur with stable dosing of controlled-release opioids or to prevent pain that occurs regularly during specific patient activities (incident pain).^{2,5}

Pain that does not require around-the-clock analgesia—such as an

episode of intermittent pain that is mild or mild to moderate, or acute pain that is mild-to-moderate and not expected to last — can be treated with acetaminophen, NSAIDs, tramadol, or short-acting opioids.¹⁸

When are controlled-release opioids specifically indicated?



It is a common misconception among healthcare providers that opioid analgesics are indicated solely for the treatment of cancer-related pain.¹⁹⁻²⁴

Use of controlled-release opioids is often not dependent on a specific disease state, but is based on the severity and the chronicity of pain. Controlled-release opioids are most often indicated for moderate to severe pain in patients requiring continuous, around-the-clock analgesia for an extended period of time, which may be weeks to months or longer. The aim is to prevent recurrence of pain by maintaining adequate analgesia.⁶

The consensus statement *The Use of Opioids for the Treatment of Chronic Pain* issued by the American Academy of Pain Medicine and the American Pain Society²⁵ and the *Model Policy for the Use of Controlled Substances for the Treatment of Pain* from the Federation of State Medical Boards of the United States¹⁰ both serve as guides for practitioners who choose to treat chronic pain with opioids.

What are the challenges associated with controlled-release opioids in terms of initiating therapy and titrating dosage?



Initiation and titration of oral opioid therapy should be individualized according to the patient's needs.^{5,6,15}

Physicians should tailor treatment using a progressive plan of pain management such as one of those outlined by the World Health Organization,²⁶ the American Pain Society,⁵ and the Federation of State Medical Boards Model Policy.¹⁰

In treating pain, it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.^{6,10} The appropriate dose for an individual patient is one that relieves pain throughout the dosing cycle without causing intolerable side effects.

A controlled-release dosing regimen should be initiated on a patient-by-patient basis, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should also be given to other relevant clinical factors.

- In patients already taking other opioids, convert from the prior opioid to an equianalgesic dose of controlled-release opioid, using an appropriate equianalgesic conversion guide. Provide immediate-release medication to be used prn for exacerbations of pain. Whenever possible, use the short-acting form of the long-acting, ATC opioid.²⁷

- * In either case, when a dose increase is needed, calculate the increase based on current total opioid dose (i.e., ATC dose + any prn doses) taken in the previous 24 hours.²⁷ Increase both ATC and prn doses.²⁷

During any period of changing analgesic requirements, including initial titration, regular communication should be maintained between the treating physician, other members of the healthcare team, the patient, and family and/or caregivers.²

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed in all patients.^{2,6,10} Dose titration may be required periodically because of the natural history of the primary disease or the development of tolerance.¹⁵

Individualized care involving titration of the opioid according to response is the best way to ensure optimal treatment for each patient. Patients should be titrated to adequate effects (generally mild or no pain); patients may also require rescue doses of supplemental analgesia.^{6,27}

Ongoing assessment should take place at regular intervals, when pain changes (worsens or new pain develops) and when treatment is changed.^{2,6,10}

Periodic reviews should assess the course of pain treatment and any new information about the etiology of the pain or the patient's state of health. Continuation or modification of controlled substances for pain management therapy depends on the physician's evaluation of progress toward treatment objectives.

When the patient no longer requires therapy with controlled-release opioids, doses should be tapered gradually, to prevent signs and symptoms of withdrawal in the physically dependent patient.⁵

When are parenteral opioids most appropriate for pain management?



Parenteral administration (e.g., intravenous or subcutaneous) of opioids benefits certain patients including those requiring rapid incremental doses of analgesia, those with persistent nausea and vomiting, with severe dysphagia or swallowing disorders and those with mental status changes accompanied by impaired ability to swallow.² Parenteral analgesia may also be more effective for patients who need high doses of oral medications requiring large numbers of tablets and for those who have undesirable side effects after each dose of a PRN medication.²

Both intraspinal and intraventricular opioid administration require implantation of a permanent device. These methods are most often reserved for intractable pain that has proved resistant to all other reasonable methods² and routes of administration.

It is important to remember, however, that established guidelines for use of analgesics in the treatment of pain support oral administration as the preferred route.^{2,5,26} Other less invasive routes, such as rectal or transdermal, should be tried when patients cannot take an opioid by mouth.² The AHRQ suggests that, “Parenteral routes should be used only when simpler, less demanding methods are inappropriate or ineffective.”²

For example, in medical emergencies such as hospital admission for rapid pain control, parenteral analgesia may be necessary,² either by continuous infusion or patient controlled analgesia. The American Pain Society Guideline for the Management of Acute Pain in Sickle Cell Disease²⁸ indicates administration of either intravenous or subcutaneous opioids upon hospital admission for severe acute pain, titrated to stable pain control then dosed around the clock.²⁸ When it is determined that a pain crisis has passed and that a patient (with sickle cell disease or rapidly escalating pain from another illness) can be maintained at home with oral medications, the IV around-the-clock opioid

dose can be used to determine conversion requirements for an oral regimen that will maintain satisfactory analgesia.²

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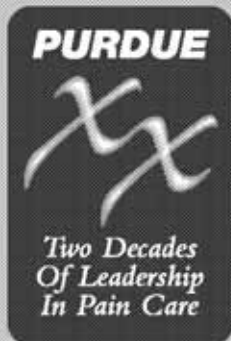


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